REMARKS

Claims 1, 2, 5 and 11-17 are pending. Claim 1 has been amended for clarity, the support for amendments being found in claim 1. No new matter has been added.

Claims 1, 2, and 5 are rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Harton et al. (Molecular and Cellular Biology, Sept. 2000; 20(17):6185-6194) in view of Lindqvist et al. (Trends in Genetics. 2002; S7-S13) and further in view of Otten et al. (Journal of Immunology. 2003; 170: 1150-1157).

The Office Action at page 11 alleges that the claimed invention would have been *prima facie* obvious in view of the cited references. We respectfully disagree with the Examiner. As previously argued in our response of April 30, 2009, the combination of cited references fails to suggest the unexpected result achieved by the invention as now claimed, and, therefore does not make the claimed invention obvious

In order to make out a *prima facie* showing of obviousness, there must be some motivation to combine the references, the combination of references must teach or suggest each and every element of the claimed invention, and there must be some reasonable expectation of success in making and using the invention as claimed. (MPEP §2141). In the present case, 1) the references cited by the Office fail to teach or suggest all of the claim limitations; 2) fail to provide the requisite motivation to combine; and 3) fail to provide a reasonable expectation of success.

1) The references cited by the Office fail to teach or suggest all of the claim limitation

None of the cited references teaches administration of at least two low doses (0.01 mg to 0.05 mg) of type II collagen to a mouse or rat resulting in a human rheumatoid arthritis phenotype in the mouse or rat. As the Examiner states on page 7 of the Office Action:

> Based on the evidence provided, the examiner accepts that it is possible to induce symptoms of arthritis with the relatively low doses of collage[sic] now present in the claim.

Because none of the cited references teaches this feature of the claims, the combination of the references cited cannot teach or suggest all the claim limitations.

"Harton teaches that increased expression of MHC class II transactivator induces pathological symptoms of Rheumatoid Arthritis." (Office Action at page 6) Harton does not teach pathological symptoms of rheumatoid arthritis in mice or rats, let alone that administering two low doses of type II collagen to mice or rats induces a rheumatoid arthritis phenotype.

"Lindqvist teach a variety of mouse models of rheumatoid arthritis. In particular, Lindqvist teach collagen induced arthritis (CIA), in which mice display symptoms similar to human rheumatoid arthritis when injected with type II collagen." (Office Action at page 8) Lindqvist does not teach or suggest administering two low doses of type II collagen to mice or rats to produce a rheumatoid arthritis phenotype.

"Lindquvist describe a transgenic mouse having cartilage-restricted expression based on a type II promoter." (Office Action at page 6). In the reference cited by Lindqvist, the transgene is used for cartilage-restricted expression of a mutant type II collagen (i.e., CII with a change at position 266) to address whether the availability of CII is important for tolerance and arthritis induction in the conventional CIA mouse model of rheumatoid arthritis. That is, Lindqvist is describing studies in which the effect of cartilage-restricted expression of mutant type II collagen in the conventional CIA model of rheumatoid arthritis. Lindqvist is not describing the generation of a mouse model of rheumatoid arthritis based on a type II collagen promoter. Apart from the CIA mouse model, Lindqvist does not teach or suggest any other mouse model of rheumatoid arthritis, much less one in which involves the cartilage-restricted expression of MHC class II transactivator (i.e., CIITA).

"Otten teach a transgenic mouse expressing CIITA in all organs and further suggest this mouse is a model for RA." (Office Action at page 6). Otten does not teach cartilage-restricted expression of CIITA (i.e., MHC class II transactivator), let alone cartilage-restricted expression of a MHC class II transactivator induced by low doses of type II collagen.

In sum, none of the cited references teaches a transgenic mouse, which when administered at least two low doses (0.01 mg to 0.05 mg) of type II collagen results develops a human rheumatoid arthritis phenotype.

2) The references fail to provide the requisite motivation to combine

There is nothing in any of the cited references or in the state of the art at the time the invention was made that provides one of ordinary skill in the art with motivation to combine the

references in the manner suggested in the Office Action. For example, in the absence of any mention of low dose administration of type II collagen in any of the cited references, there is no motivation to combine the cited references to arrive at Applicants' invention. Assuming for the sake of argument that there were such motivation, the combination does not teach or suggest each and every element of the claimed invention ***because none of the references teaches or suggests low dose administration of type II collagen.***

3) The references fail to provide a reasonable expectation of success

Because the combination of the cited references do not teach or suggest each and every element of the claimed invention, one would have no expectation of success in arriving at Applicants' claimed invention based on these disclosures. It would not be possible to arrive at Applicant's transgenic mouse, at least because none of the cited references teaches low dose administration of type II collagen inducing rheumatoid arthritis in a mouse or rat.

The present inventors have generated a transgenic mouse with a transgene comprising a type II collagen promoter and an MHC class II transactivator gene to express this gene in cartilage. In contrast, forced expression of the MHC class II transactivator gene alone did not show any phenotype similar to human rheumatoid arthritis spontaneously.

Surprisingly, the transgenic mouse showed pathologic conditions of human rheumatoid arthritis by the induction using a very small amount of type II collagen such as 0.01 mg to 0.05 mg. Namely, it was revealed that the transgenic mouse acquired a high susceptibility to a foreign antigen. In contrast, *such a small dose amount of the type II collagen cannot induce the pathologic conditions of human rheumatoid arthritis satisfactorily* in the H-2^q haplotype mouse, which is conventionally used as a model animal of human rheumatoid arthritis. The present invention would never be achieved without this *unexpected result.* ***The combination of references cited in the rejection do not at all suggest the unexpected result of such a small dose amount of the type II collagen.***

Even so, the rejection has questioned the scientific contribution and/or inventiveness of Applicants' transgenic mouse. The Office Action at page 7 states:

> However, the examiner is left to ask himself, how has this knowledge advanced science or what is the inventive feature of inducing Rheumatoid Arthritis symptoms in a mouse using only a low dose of collagen.

In response, Applicants respectfully submit that the transgenic mouse or rat of the invention shows excellent features in comparison with conventional animal models, e.g., the CIA mouse model, as described in the specification. Relevant portions are quoted (emphasis added):

> In other words, the TG animal of the present invention has ***higher sensitivity showing the pathologic conditions*** of human rheumatoid arthritis than the H-2^q haplotype mouse that has been conventionally used as a model animal of human rheumatoid arthritis. [0097]
>
> As a result, in general CIA, in several days after the secondary immunization is carried out, strong redness and swelling are observed. While in the transgenic mouse, redness and swelling in the extremities have been observed for several weeks or more (FIG. 2). [0157]
>
> When about two months had passed, the swelling in the extremities progressed further. Although some individuals showed slight remission, basically bone destruction progresses, so that disorders such as bone deformity were observed finally (FIG. 6). [0158]
>
> In a conventional CIA method, at the fifth week following the immunization, the change of the bone density was observed, and large change was not shown thereafter. On the other hand, in the ***transgenic mouse, not only the progress of inflammation but also the change in the bone density progresses gradually.*** [0159]
>
> For example, primary lesion of the respiratory organ, vasculitis, reduction of red blood cell count, which are caused by rheumatism, are confirmed. [0160]

Thus, the transgenic mouse being claimed is distinct from the conventional CIA mouse model. That is, Applicants' transgenic mouse advantageously and more closely models the pathologic conditions of human rheumatoid arthritis compared to a prior art mouse model of rheumatoid arthritis. The deficiency of the CIA mouse model is at least evidenced in Lindqvist,

which was cited by the Examiner. For example, Table 2 of Lindqvist shows that the CIA mouse model does not present all the criteria of classification by the American College of Rheumatology (ACR).

Moreover, using a low dose of collagen in a mouse model of rheumatoid arthritis reduces any potential CIA response, which, as set forth above, does not represent the pathologic conditions to the extent of the transgenic mouse being claimed. Therefore, Applicants' transgenic mouse is a specific and robust model for human rheumatoid arthritis.

In conclusion, Harton, Lindqvist, and Otten do not teach all the elements of a transgenic mouse as claimed, nor do they provide the requisite motivation or guidance to combine the three references in the manner suggested by the Office Action, and thus do not provide an expectation of success in making and using the invention.

Importantly, none of the cited references provides insight into the surprising and unexpected results observed by Applicants, which showed administration of a relatively low dose of collagen II can induce pathologic conditions of rheumatoid arthritis in mice or rats. This result was unexpected because none of the references present any data indicating that low dose of collagen II would be effective to induce rheumatoid arthritis in mice.

In view of the above amendment, applicant believes the pending application is in condition for allowance. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105.

Respectfully submitted,

Dated: September 11, 2009

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